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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,631	12/17/2001	Maurits W. Geerlings	1000780-00002	1753

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EXAMINER	
LUM, LEON YUN BON	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,631	GEERLINGS, MAURITS W.	
	Examiner	Art Unit	
	Leon Y. Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-43* is/are pending in the application.

4a) Of the above claim(s) *30-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 5, 2006 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 26 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of Rotmensch et al (Gynecologic Oncology, 1990 [abstract]), van Geel et al (US 5,355,394), and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986).

In the instant claim, Macklis et al reference teaches a ^{212}Bi-labeled radioimmunoconjugate, wherein ^{212}Bi is bound to a monoclonal antibody conjugated to the chelating agent diethylenetriaminepentaacetic acid (i.e. coupling radiolabel to a targeting moiety to form a conjugate), and wherein the ^{212}Bi-labeled radioimmunoconjugate is highly efficient at eradicating Thy 1.2^{+} EL-4 murine lymphoma cells *in vivo* (i.e. target cells; administering said conjugate to a mammal; diseased cells), and that the cytotoxicity is antigen selective (i.e. ligand having binding specificity for a receptor associated with said target cell). See page 1024, left column, 2nd paragraph to middle column, 2nd paragraph.

However, Macklis et al fail to explicitly teach that the target cells are in micrometastases having a diameter of about 1 mm or less, and also fail to teach the steps of providing a sufficient quantity of ^{225}Ac to produce a therapeutically effective amount of ^{213}Bi through radioactive decay, binding the ^{225}Ac onto a substrate for immobilizing ^{225}Ac, eluting from the substrate ^{213}Bi produced by bound ^{225}Ac, and that the radiolabel coupled to the targeting moiety is ^{213}Bi, substantially free of ^{225}Ac.

Rotmensch et al teach radiolabeled monoclonal antibodies against ovarian micrometastases, in order to treat intraperitoneal metastases from ovarian and other gynecologic tumors that area a significant source of current treatment failure, wherein the radiolabel can be alpha particle emitters. See abstract.

Van Geel et al reference teaches the production and recovery of ^{213}Bi from ^{225}Ac, in order to obtain a radionuclide that (1) has a short half-life on the order of hours and (2) does not induce radiation-strain on the patient, an effect attributed to currently used radionuclides such as ^{212}Bi. See column 1, lines 7-8 and 15-20; and column 2, lines 48-52; and Figure 1.

Kozak et al reference teaches eluting α-particle emitters from nuclide generators held by resin in a polyethylene column, in order to provide a means for easily obtaining α-particle emitters using a disposable device. See page 263, left column, 2nd paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al with radiolabeled monoclonal antibodies against ovarian micrometastases, as taught by Rotmensch et al, order to treat intraperitoneal metastases from ovarian and other gynecologic tumors that area a significant source of current treatment failure. The ability to produce more successful treatment of ovarian and other gynecological tumors through containing their metastases provides the motivation to combine the teaching of Rotmensch et al with the method of Macklis et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the step of

Rotmensch et al in the method of Macklis et al, since Macklis et al teach the general efficacy of radioimmunotherapy using alpha-particle-emitting immunoconjugates, and the radiolabeled monoclonal antibodies against ovarian micrometastases taught by Rotmensch et al are one type of immunoconjugates that can by applied using the method of Macklis et al.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al with the production and recovery of ^{213}Bi from ^{225}Ac, as taught by van Geel, in order to obtain a radionuclide that has a short half-life on the order of hours and does not induce radiation-strain on the patient. The ability to destroy tumors while providing the benefit of a medically safer radionuclide provides the motivation to combine the decay step and ^{213}Bi radionuclide of van Geel with the method of Macklis et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in substituting the ^{213}Bi of van Geel for the ^{212}Bi of Macklis et al, because the disclosed radionuclides in both references are alpha-particle emitters applied for the same purpose and in the same manner.

It would further have been obvious to modify the method of Macklis et al with the step of eluting α-particle emitters from nuclide generators held by resin in a polyethylene column, as taught by Kozak et al, in order to provide a means for easily obtaining α-particle emitters using a disposable device. The advantages of an easier technique to obtain alpha emitters and a disposable device to prevent spreading of contamination provide the motivation to combine the teachings of Kozak et al with the

method of Macklis et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining the step of Kozak et al in the method of Macklis et al, since the step of Kozak et al simply provides a way of obtaining an α-particle emitter, and the ^{212}Bi of Macklis et al is one type of an α-particle emitter.

Furthermore, since it has been established supra that it would have been obvious to substitute ^{213}Bi for ^{212}Bi, wherein ^{213}Bi can be applied to treat metastatic ovarian tumors, and wherein ^{213}Bi is derived from the nuclide generator ^{225}Ac, one of ordinary skill in the art at the time would have had a reasonable expectation of success in combining all teachings of Macklis et al, Rotmensch et al, van Geel, and Kozak et al to read on the instant claims. The combination of references thereby results in a process of deriving ^{213}Bi from ^{225}Ac (van Geel) by fixing the ^{225}Ac on a resin in a polyethylene column and collecting ^{213}Bi generated from the immobilized ^{225}Ac (Kozak et al), and conjugating the ^{213}Bi to an antibody and delivering the conjugate *in vivo* for attachment to cancer cells (Macklis et al), wherein the cancer cells are ovarian micrometastases (Rotmensch).

5. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of van Geel et al (US 5,355,394), Rotmensch et al (Gynecologic Oncology, 1990 [abstract]), and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Greer (US 4,894,364).

Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al references have been disclosed above, and Macklis et al additionally teach the step of injecting two to four doses over four to eight hours, wherein most of the animals treated with 150 or 230 μCi were cured of their tumor burden (i.e. conjugate administered intermittently in fractions of the total amount required kill said target cells, and a sufficient number of fractions of sufficient quantities are administered to kill essentially all target cells). See page 1024, middle column, 2nd paragraph; and 1025, right column, 1st paragraph. However, Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al fail to teach that the total quantity of α radiation administered to the mammal is less than the total quantity necessary to kill essentially all target cells by administering a single dose of said conjugate.

Greer reference teaches administering repeated dosages with less total irradiation to achieve effective tumor kill, in order to provide a method that results in long term cures as opposed to only partial remission. See column 11, lines 59-66.

The advantage of a complete cure provides the motivation to combine the teachings of Greer with the method of Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of repeated dosages with less total radiation, as taught by Greer, in the method of Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al, since Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al teach radioactive elimination of tumor cells, and the

repeated dosages with less total radiation taught by Greer is also used to destroy tumor cells.

6. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of Rotmensch et al (Gynecologic Oncology, 1990 [abstract]), van Geel et al (US 5,355,394), and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claim 26 above, and further in view of Turner (US 5,296,216).

Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al references have been disclosed above, but fail to teach that said conjugate is administered continuously for a time sufficient to administer an effective amount of ^{213}Bi for killing said target cells in the mammal, and wherein a sufficient duration of continuous administration is maintained to kill essentially all target cells bound by said conjugate.

Turner teaches administering radiotherapy with a continuous intravenous infusion for five days, in order to prevent recurrence of cancer after surgical removal of cancer. See column 6, lines 3-14.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al with the step of administering radiotherapy with a continuous intravenous infusion for five days, as taught by Turner, in order to prevent recurrence of cancer after surgical removal of cancer. The advantage of ensuring a complete recovery from cancer provides the motivation to combine the step of Turner with the method of Macklis

et al, Rotmensch et al, van Geel et al, and Kozak et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including the step of continuous intravenous infusion for five days, as taught by Turner, in the method of Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al, since Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al teach radioactive elimination of tumor cells, and the continuous infusion taught by Turner also eliminates tumor cells.

7. Claims 29 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macklis et al (Science, vol. 240, pp. 1024-1026, 1988) in view of Rotmensch et al (Gynecologic Oncology, 1990 [abstract]), van Geel et al (US 5,355,394), and Kozak et al (Tibtech, vol. 4, no. 10, pp. 259-264, 1986) as applied to claims 26 and 39-42 above, and further in view of Zamora et al (US 5,443,816).

Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al references have been disclosed above, but fail to teach that said ligand is a peptide.

Zamora et al reference teaches peptides that can be conjugated to a medically useful, radioactive metal ion, including bismuth, and that can be applied in vivo, in order to provide a molecule that can be frozen or lyophilized and maintained for an indefinite period before labeling with the medically useful metal ion. See column 3, lines 36-42; column 4, lines 39-47; column 9, lines 17-20; and column 20, lines 21-29.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Macklis et al, Rotmensch et al, van Geel et al, and

Kozak et al with peptides that can be conjugated to a medically useful, radioactive metal ion, including bismuth, and that can be applied in vivo, as taught by Zamora et al, in order to provide a molecule that can be frozen or lyophilized and maintained for an indefinite period before labeling with the medically useful metal ion. The advantage of being able to stockpile and store treatment materials provides the motivation to combine the step of Zamora et al with the method of Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including peptides that can be conjugated to radioactive metal ions, as taught by Zamora et al, in the method of Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al, since Macklis et al, Rotmensch et al, van Geel et al, and Kozak et al teach targeting moieties bound to an α-particle emitting radioisotope for radiotherapy in vivo, and the peptide taught by Zamora et al is one type of targeting moiety that can be bound to bismuth, which is a type of α-particle emitting radioisotope , and can also be applied in vivo.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 26-29 and 39-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,641,471. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 of the copending application recite the limitations of claims 26-29 and 39-43 of the instant application, including the steps of killing micrometastases target cells by providing a sufficient quantity of ^{225}Ac immobilized on a binding medium (i.e. substrate) to produce an effective amount of ^{213}Bi, eluting and coupling the ^{213}Bi to a an antibody targeting moiety (i.e. ligand having binding specificity for receptor associated with said target cell), and administering the conjugate to a mammal to permit the conjugate to contact the target cells (i.e. effectuate specific binding).

Response to Arguments

10. Applicant's arguments with respect to claims 26-29 and 39-43 have been considered but are moot in view of the new ground(s) of rejection.

With respect to the judicially created doctrine of obviousness-type double patenting over claims 1-11 and 20-22 of U.S. 6,403,771, this rejection has been withdrawn due to Applicant's amendment of the instant claims.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on weekdays from 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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